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Signals from fat after injury: Plasma adipokines and ghrelin concentrations in the severely burned ☆

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ABSTRACT

Introduction: Hypermetabolism is universal in the severely burned and is characterized by catabolism of lean mass and body fat with associated insulin resistance. Adipokines are likely to play a role in these changes but have not been identified to date in burn patients.
Methods: From a single burn ICU, 17 burn patients with an expected stay >14 days were studied. Study period began within 14 days of admission. Over 7 days, plasma samples were collected for measurement of leptin, adiponectin, resistin, ghrelin, insulin, and cortisol by ELISA. For comparison, samples from 15 healthy controls of similar age, BMI, and blood glucose were obtained.
Results: Mean age was 33 ± 17 years and BMI 26 ± 3.4. Average burn size was 45 ± 20% TBSA and ISS 32 ± 10 with 72% having inhalation injury; in-hospital mortality was 29%. Estimated energy needs were 3626 ± 710 kcal, of which 84 ± 21% were met by enteral feeding with intensive insulin treatment (glucose 80–110 mg/ml). Using the homeostasis model assessment of insulin resistance, burned subjects were more resistant than controls (17 ± 11.3 and 8 ± 10.0). Insulin levels were elevated (57 ± 35.6 μU/ml in burned subject vs. 26 ± 31.1 μU/ml in controls), and cortisol concentrations increased (50 ± 41.2 μg/dl vs. 12 ± 3.9 μg/dl). These traditional hormone changes were associated with increased resistin (16.6 ± 5.5 ng/ml vs. 3.8 ± 0.9 ng/ml) and decreased leptin (8.8 ± 8.9 ng/ml vs. 19.4 ± 23.5 ng/ml), adiponectin (9 ± 3.5 ng/ml vs. 17 ± 10.2 ng/ml), and ghrelin (0.37 ± 0.14 ng/ml vs.0.56 ± 0.26 ng/ml).
Conclusion: Patients with burns, who are characteristically hypermetabolic with hypercortisolism and insulin resistant, have significant changes in adipokine levels that appear independent of the magnitude of initial injury or metabolic derangement. In addition, suppression of ghrelin in the presence of decreased leptin and adiponectin levels in combination with increased insulin and resistin levels represent unexpected changes in the metabolic milieu of the injured patient possibly due to dramatic activation of inflammatory pathways, indicating strategies for treatment.

1. Introduction

Over the past two decades, adipose tissue has become recognized as an endocrine organ [1–3]. The factors released by this organ have been termed adipokines, which have been demonstrated to play roles in the regulation of energy balance, insulin resistance, inflammatory responses, and endothelial function. Among the adipokines; leptin, adiponectin and resistin are currently the most prominent as a result of their functions in obesity. Caloric restriction results in decreases in leptin and resistin and an increase in adiponectin levels. Recently, adipokines have also been implicated in observed changes in the course of critical illness in response to inflammation and inadequacy of nutritional support [4]. Adiponectin is reduced in ICU patients and associated with increases in inflammatory markers, such as cortisol and C-reactive protein [5]. In critically ill patients, increases in resistin have been correlated with a range of inflammatory parameters and associated with unfavorable outcomes, including death [6]. Decreases in leptin and adiponectin and increases in resistin have been independently associated with increases in insulin resistance [6,7]. The majority of these studies have focused on a single adipokine at a time in patients. Recently, in animal models of burns, significant

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alterations in adipokines have been reported, and interventions to attenuate these responses have been associated with improved outcomes [8–10]. Increasing evidence of alterations in adipokines in critically ill patients and promising interventional studies in animals have led to a rethinking of the role of adipose tissue in the care and outcome of the critically injured patient, with the possibility of novel therapeutic interventions.

Patients with burns embody an extreme version of the metabolic dysregulation that occurs in critical illness [11–14]. Metabolism increases by over 50%, resulting in significant catabolism of fat and lean mass. Additionally, there is a high prevalence of insulin resistance associated with alterations in substrate metabolism in this patient population. Patients with burns also have a significant inflammatory response coupled with high rates of infection. Therefore, adipokines are likely to be significantly changed after burn. For these reasons, we assessed the responses of multiple adipokines, as well as the gut hormone ghrelin, in severely injured patients with burns in an effort to determine their relationships with metabolism, inflammation, and insulin resistance. We hypothesized that the magnitude of injury due to burns would be associated with changes in adipokine concentrations in relation to the levels in normal subjects, which would in turn be correlated with alterations in metabolism, inflammation, and insulin resistance.

2. Materials and methods

After approval was obtained from the Brooke Army Medical Center institutional review board, patients admitted to a single burn ICU and a comparison control group of non-fasted healthy volunteers were enrolled in the study. All subjects enrolled in this study provided written informed consent, and, when necessary, patient consent was obtained through their legally authorized representative.

2.1. Burn subjects

Patients admitted to the burn center with a burn size of >20% of total body surface area (TBSA), at least 18 years of age, expected to stay a minimum of 2 weeks (per estimation of treating physician), on the intensive insulin therapy (IIT) protocol, and having an arterial line for blood collection access were rendered eligible for the study. Exclusion criteria included: cerebral arterial injury, history of clinically diagnosed hypoglycemia, pregnancy, and a history or high risk of seizures.

Study subjects were adults receiving treatment between February 2007 and December 2007 at the US Army Institute of Surgical Research for burns. Subjects consisted of both military and civilian personnel, which we have previously compared and found no differences in outcome following adjustment for age differences [15]. The study period concentrated on the first 14 days of patient hospitalization. In addition to recording admission demographics such as age, sex, body mass index scores (BMI), inhalation injury (yes or no), pre-existing diabetes (yes or no) and heart diseases (yes or no), number of ICU days, days on mechanical ventilator, and length of hospital stay were collected.

2.2. Outcome measurements

2.2.1. Metabolism

In the course of the care, an extensive effort was made to meet the metabolic requirements of the burn subject. Metabolic requirements were calculated using the Carlson equation [16]. All subjects were fed enterally based on the calculated amount of daily calories. The ratio of caloric intake to caloric requirement was used to assess the metabolic status of the burn subjects.

2.2.2. Inflammation

As indices of the inflammatory state of the burn subjects, Multiple Organ Dysfunction Score (MODS) was calculated, and plasma cortisol concentrations were measured. Plasma cortisol is associated with the extent of illness and characterizes the inflammatory state of the patient [17]. MODS was determined daily, and the average over the course of the study for each subject was used. A MODS provides an objective measure of organ dysfunction during the course of an ICU stay and is indicative of the severity of illness.

2.2.3. Insulin resistance

Since all enrolled subjects were on IIT, hourly glucose readings from a point-of-care (POC) glucometer (SureStep™ Flexx, LifeScan, Milpitas, CA) were available as well as laboratory glucose values. Arterial blood glucose levels were measured using the POC glucometer and corrected for hematocrit [18]. Units of insulin administered were recorded, and total daily sum calculated. To assess insulin resistance, plasma concentrations were assayed via ELISA to quantify amounts of circulating insulin. Severity of insulin resistance was calculated with a modified version of homeostasis model assessment of insulin resistance (HOMA-IR) formula by using average glucose and average circulating insulin levels of subjects. In this study, HOMA-IR was used to assess severity of insulin resistance rather than as a tool for an exact quantitative measure of physiologic condition. As the IIT was in use, glucose was clamped within a uniform range, and so, the daily insulin administered was also indicative of insulin resistance.

2.2.4. Subject data

Age, sex, height, weight, and calculated individual body mass index (BMI) were recorded. Glucose measurements were obtained with the standard-of-care glucometer used in the burn ICU. As the burn subjects were on continuous feeds, food intake of the control subjects was not restricted. Control subjects were selected if their glucose concentrations were within the range (80–145 mg/dl) previously described for our patient population [18].

2.3. Blood samples

Subjects in the study were all severely injured with burns, and survival was dependent on required critical care. By virtue of patient condition, clinical care, high nutritional demands and IIT, it was neither clinically feasible, nor prudent, to obtain fasting levels. The intent was to collect arterial blood three times a day (morning, noon, and night) for a minimum of 7 days, or up to the day of death during opportunistic periods when the subjects had not recently undergone surgery, wound care, rehabilitation or other procedures. Samples were centrifuged, and plasma aliquotted for later analysis. A one-time venous blood collection (12 ml) was taken from each control subject, centrifuged, and the plasma aliquotted for later analysis.

2.4. Plasma assays

Plasma collected from whole blood samples was stored at −80 °C for later analysis. Commercial plasma enzyme-linked-immunosorbent assays (ELISA; Linco Research, St. Charles, MO; Neogen Corp, Lexington, KY) were used to measure insulin, leptin, ghrelin, adiponectin, cortisol, and resistin.

2.5. Statistical analysis

Statistical analysis was done with SPSS version 16.0 (SPSS Inc., Chicago, IL) and SigmaPlot 11.0 (Systat Software Inc., San Jose

Table 1
Demographics of control and burn subjects. Values in the table are mean ± standard deviation (median [inter-quartile range]).

	Control subjects (n = 15)	Burn subjects (n = 17)
Age (yr)	37 ± 11.2 (36[32–41])	33 ± 16.7 (27[21–35])
% Male	60	82
Height (cm)	173 ± 12.7 (175[165–182])	176 ± 11.1 (175[168–183])
Weight (kg)	82 ± 19.4 (80[70–92])	82 ± 12.8 (81[71–88])
Body mass index	27 ± 5.1 (26[23–31])	26 ± 3.4 (26[24–27])

CA). For categorical data, the chi-square test was used. An unpaired Student's t-test was performed for comparisons of means between patients and volunteers. Correlations were determined by simple linear regression. When the test for homogeneity was not met, data was transformed to a natural logarithm. Correlation coefficient ranges were defined as: $r < 0.4$, weak; $0.4 \leqslant r \leqslant 0.7$, moderate; $r > 0.7$, strong. A p-value of less than 0.05 was considered to be a significant finding. Values within the text are reported as mean ± standard deviation.

3. Results

Seventeen burn subjects were enrolled 7 ± 2.5 days post-admission to the ICU, and individual study periods lasted 7 ± 2.7 days. For the study population, averages for TBSA, injury severity score (ISS) and MODS were 45 ± 20%, 33 ± 178%, and 8 ± 2.6%, respectively. Subjects averaged 19 ± 20 days on a ventilator, 33 ± 20.7 days in the ICU, and 63 ± 38.5 overall in-hospital days. The in-hospital mortality rate was 29%. Based upon American Burn Association Guidelines [19]; 67% of burn subjects had positive pneumonia cultures, all subjects were septic at some point within the study period, and all met the criteria for systemic inflammatory response syndrome (SIRS). Seventy-one percent (12/17) of burn subjects sustained inhalation injuries. Thirty-five percent of subjects (6/17) were on glucocorticoid therapy, and all received oxandrolone. There was no difference in the plasma cortisol levels between treated and untreated patients, 56 ± 51.3 and 47 ± 24.2 ng/ml, $p = 0.63$. Medical histories revealed four cases of pre-existing conditions. Two subjects had annotations of diabetes mellitus, and two others had heart disease.

During the study period, an average of 18 ± 9 blood samples per burn subject were obtained and subsequently analyzed. Data for a subject was averaged for comparison with control subjects' values. Burn subjects were contrasted to control subjects with a similar demographic profile (Table 1). Glucose concentrations were also similar at 123 ± 10.7 ng/ml (burn subjects) and 124 ± 14.3 ng/ml (control subjects).

3.1. Metabolism

The calculated total energy needs of burn subjects were 3626 ± 710 calories per day, which was elevated when compared to controls that required 2089 ± 343 calories. For the burn subjects, average total nutrition support was 3002 ± 849 calories; thus, burn subjects met a median of 93% of their nutritional requirements through feeding.

3.2. Inflammation

The plasma cortisol concentrations of burn subjects were on average 406% higher than controls (Table 2). Plasma cortisol levels were also associated with MODS ($r = 0.57$, $p < 0.02$). The burn subjects were considered to be in a hyper-inflammatory state based upon the high incidence rates of sepsis, positive pneumonia cultures, MODS and the increased plasma cortisol concentrations.

3.3. Insulin resistance

In the absence of differences in plasma glucose concentrations, plasma insulin levels in the burn subjects were 217% higher than controls (Table 2). Thus, based on the HOMA-IR, burned subjects were more insulin resistant than controls (Table 2). As all of the burn subjects were on IIT and glucose levels were controlled, the HOMA-IR was highly correlated with the concentration of plasma insulin ($r = 0.91$, $p < 0.001$). Therefore, plasma insulin was subsequently used as an indicator of insulin resistance. In the burn subjects, the daily insulin use was 113 ± 54.7 units per day. Plasma insulin and daily insulin administration were moderately correlated ($r = 0.58$, $p < 0.01$), and daily insulin administration was moderately correlated with plasma cortisol ($r = 0.52$, $p < 0.03$).

3.4. Adipokine concentrations

Plasma levels of leptin, adiponectin, and the gut hormone, ghrelin, were all lower in burn subjects when compared to controls (45%, 55%, and 66%, respectively, Table 2). Associations between leptin and apiponectin plasma concentrations and inflammatory markers, indications of metabolism, and insulin resistance were not found. However, leptin concentration showed a moderate correlation with BMI ($r = 0.52$, $p < 0.04$). There was also a moderate correlation of ghrelin levels with percent of metabolic needs met ($r = 0.57$, $p < 0.02$) and daily insulin administration ($r = 0.51$, $p < 0.01$). Ghrelin levels were also moderately correlated with ISS ($r = 0.54$, $p < 0.02$) and leptin concentrations ($r = 0.65$, $p < 0.01$) (Fig. 1).

In burn subjects, the plasma resistin levels were 436 ± 143% higher than controls (Table 2). Resistin was not associated with indices of metabolism or insulin resistance, but it was moderately correlated with MODS ($r = 0.61$, $p < 0.01$) (Fig. 2).

4. Discussion

Severely burned subjects are in a hypermetabolic state associated with loss of lean and fat body mass during their ICU course [11–14]. Extensive measures are used to attenuate the catabolic state after burn, including the use of anabolic steroids, growth hormones, beta blockers and intensive insulin therapy. Furthermore,

Table 2
Plasma concentrations of control and burn subjects. Values in the table are mean ± standard deviation (median [inter-quartile range]).

	Control subjects (n = 15)	Burn subjects (n = 17)	p-Value
Cortisol (ng/ml)	12 ± 3.9 (13[9.1–15.9])	50 ± 41.2 (35[23.0–54.7])	<0.002
Insulin (μU/ml)	26 ± 31.1 (14[9.1–22.6])	57 ± 35.6 (42[35.4–81.4])	<0.02
Glucose (ng/ml)	124 ± 14.3 (126[117–134.5])	123 ± 11.0 (123[113.1–128.8])	>0.80
HOMA	18 ± 12.5 (12.1[10.69–24.79])	8 ± 10.0 (3.6[2.64–7.28])	<0.03
Leptin (ng/ml)	19.4 ± 23.55 (10.7[6.35–20.46])	8.8 ± 8.9 (5.2[1.62–13.57])	<0.04
Adiponectin (ng/ml)	16.7 ± 10.2 (14.4[9.8–19.8])	9.2 ± 3.53 (8.5[6.46–11.05])	<0.01
Resistin (ng/ml)	3.8 ± 0.94 (3.6[3.28–4.21])	16.6 ± 5.47 (14.5[12.9–19.0])	<0.001
Ghrelin (ng/ml)	0.56 ± 0.257 (0.56[0.333–0.705])	0.37 ± 0.141 (0.338[0.276–0.435])	<0.02

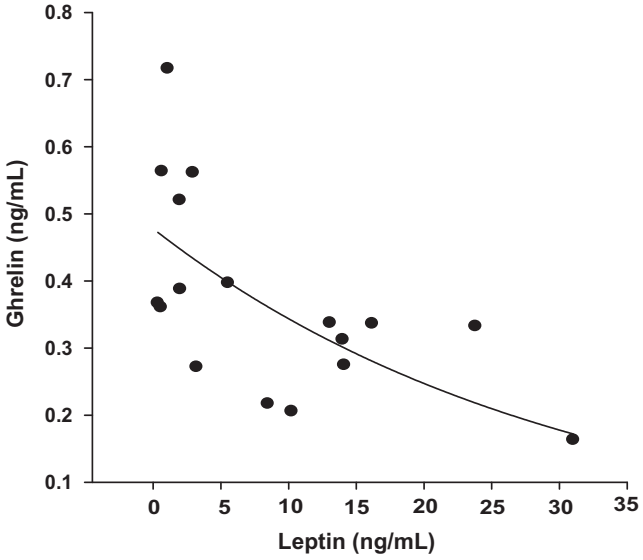

Fig. 1. The association of leptin and ghrelin in patient with severe burns ($r = 0.65$, $p < 0.01$).

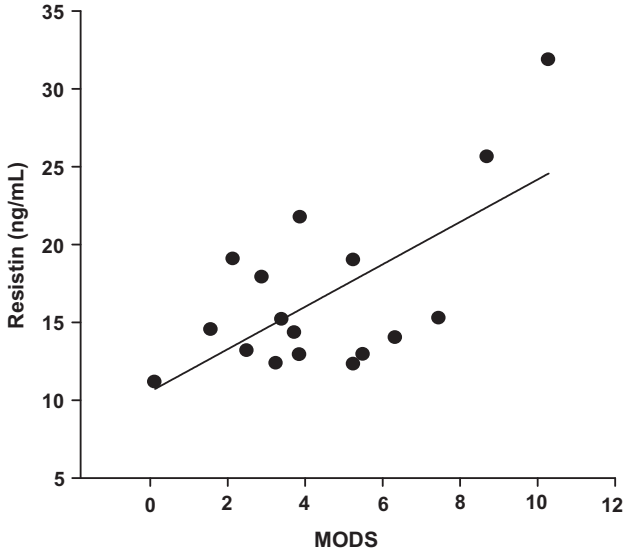

Fig. 2. The association of MODS and resistin in patient with severe burns ($r = 0.61$, $p < 0.01$).

close monitoring of feeding is undertaken to meet the nutrition needs of the patient. All of which were employed in our burn subject population. In spite of these efforts, a hypermetabolic state in conjunction with insulin resistance and a hyper-inflammatory state, may persist for years after injury [12,13].

Plasma cortisol is increased in the critically injured patient and has been related to the degree of illness [17,20]. In the present study, cortisol concentrations of burn subjects were increased compared to controls and found to be moderately correlated with the degree of illness, as indicated by MODS. Cortisol levels were not related to the size of the burn or ISS. This supports the suggestion that the increase in cortisol is due to factors reflective of MODS during the flow phase post burn [17,21].

Recently, adipose derived hormones have been demonstrated to play major roles in the regulation of metabolism [1–3]. They have also been implicated in insulin resistance and in the inflammatory response. The preeminent adipokine is leptin whose concentrations rise with increasing fat mass and decrease with caloric restriction and reductions in fat mass [22]. Leptin has been characterized as a satiety hormone. Previous studies of critically ill patients, as well as patients with burns, have demonstrated leptin levels to be reduced [23]. A similar decrease was noted in the present study. Leptin was also not correlated with any of the indices of insulin resistance in burn subjects, which was in agreement with the findings of others [23]. However, in a dissenting study, Langouche et al. reported a reduction in leptin, which was weakly correlated ($r = 0.29–0.37$) with insulin resistance [7].

Adiponectin, in contrast to leptin, is negatively associated with body fat mass and has been deemed an orexigenic hormone [22]. In critically ill patients, Venkatesh et al. reported adiponectin levels to be decreased to 57% of controls and to be strongly correlated with plasma cortisol [5]. We noted a similar decrease but failed to identify an association with cortisol or MODS. Of interest, is the lack of an association of the reduction of adiponectin with indices of insulin resistance. In the metabolic syndrome and type 2 diabetes, a reduction in adiponectin is related to an increase in insulin resistance. Langouche and colleagues have previously reported that transiently low adiponectin levels in critically ill patients are associated with insulin resistance [7]. This association may be overshadowed by other factors regulating insulin resistance in burn subjects [14].

Studies of resistin in critically ill patients are limited. Duffy et al. found resistin to be 278% higher than controls in children with burns [24]. Koch et al. also found resistin concentrations to be increased and to a greater extent in patients with sepsis [6]. In the present study, resistin was significantly increased by over 400% compared to controls. Importantly, all of the burn subjects had sepsis at some point during the study period. Furthermore, resistin was correlated with the MODS, suggesting a relationship of resistin to inflammatory processes (Fig. 2). Duffy and colleagues reported in burned subjects, resistin levels increased in parallel with insulin dysfunction; though within our burn patients, an association of resistin with insulin resistance could not be identified [24]. Resistin appears to be increased in subjects with burns and is associated with the degree of illness and the inflammatory state of the patient.

Ghrelin is synthesized in the gut and has been determined to be involved in the regulation of food intake and energy homeostasis, and classified as an orexigenic hormone [25]. Additionally, ghrelin has been suggested to play a role in endothelial permeability, modulation of pro-inflammatory cytokines, and the stimulation of growth hormone release. Information as to the response and actions of ghrelin in critically ill patients is limited. Ghrelin levels in critically ill patients have been reported to be decreased as well as increased compared to controls [26,27]. We found in burn subjects that ghrelin was decreased compared to controls and associated with nutritional needs met, as well as leptin concentrations (Fig. 1). The difference in the findings between studies may be attributed to the aggressive attempts to adequately feed our subjects in response to the hypermetabolic state that is associated with burns. In the present study, the burn subjects met a median of 93% of their nutritional needs, far exceeding the average of 60% observed in most intensive care units [4]. Ghrelin is increased with caloric restriction, and this may account for the increase found in other studies. As ghrelin was not associated with the inflammatory status of the patient or insulin resistance, it may provide an indicator of the adequacy of feeding to meet the nutritional needs of the critically injured patient.

The present study encompasses the response of adipokines and ghrelin in burn subjects during the acute phase immediately

following injury. The lack of association of these hormones with burn size and ISS implies that the changes are indicative of the ICU course rather than the degree of the initial injury or that a burn of greater than 20% TBSA elicits a maximal response. The scope of the present study does not cover the post injury period. As noted earlier, patients with burns sustain a state of hypermetabolism, hyperinflammation, and abnormal insulin sensitivity for years following injury [12,13].

Recent animal studies of burns and sepsis have alluded to the possibility that interventions to attenuate the responses of adipokines and ghrelin may be beneficial in the care of the burn patient [8–10,28]. Administration of ghrelin after burns has been suggested to inhibit muscle protein breakdown, stimulate growth hormone release, depress neutrophil infiltration and release of pro-inflammatory cytokines, and contribute to increased food intake [8]. Suppression of adiponectin promotes endothelial activation, increases proinflammatory cytokines, and profoundly exacerbates mortality due to sepsis, while replacement attenuates these responses [28]. Administration of leptin post-burn is suggested to decrease inflammation, attenuate multiple organ failure and increase wound tissue angiogensis [9,10]. In light of these findings, defining the responses of these hormones in critical illness offers opportunities for new interventions.

The burn population used in this study is unique as it represents the extreme in metabolic and inflammatory derangements, thus the transfer of these findings to other populations maybe limited. There were also a limited number of subjects, and the study was conducted within the constraints of clinical care. To limit some of these influences, we attempted to obtain blood samples during periods where clinical interventions were minimized; however, this was not always possible, and the impact of care interventions on the hormones studied are not known. Despite the aforementioned limitations the observed responses were comparative to those reported in other ICU populations.

This is the first study to attempt to evaluate the response of various adipokines and ghrelin simultaneously in burn subjects. The reduction of both leptin and adiponectin in patients with burns is counterintuitive, based on previous data in obesity and malnutrition, and therefore warrants further investigation. The association of resistin with the inflammatory state of the patient and ghrelin with nutritional needs met, puts forth unique possibilities to assess the status of the patient through the use of these hormones as biomarkers. This work also provides the basis on which to cultivate clinically relevant animal models to evaluate novel therapeutic interventions, presently being developed for the treatment of metabolic syndrome that can be translated to the care of the critically injured patient.

Disclosure statement

The authors have no conflicts of interest to declare. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the US Department of Defense or the US Government. Some of the authors are employees of the US Government.

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